Pharmacologic management of herpes zoster and postherpetic neuralgia

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SUMMARY

Herpes zoster is an infection caused by reactivation of dormant varicella-zoster virus. The acute course of herpes zoster is generally benign; however, some patients will experience postherpetic neuralgia characterized by severe, relentless, and at times disabling pain that is often refractory to treatment. While herpes zoster responds to acyclovir, cost-benefit considerations limit the drug's usefulness to only a select group. Postherpetic neuralgia requires a holistic approach, including pharmacologic therapy using several different classes of drugs.

RÉSUMÉ

Le zona (herpes zoster) est une infection causée par la réactivation de la phase dormante de l'herpes virus varicellae. Le zona est une infection aiguë dont l'évolution est habituellement bénigne mais certains patients souffriront d'une névralgie postzostérienne caractérisée par des douleurs intenses et continuelles, parfois incapacitantes, et qui sont souvent réfractaires à tout traitement. Bien que le zona puisse répondre à l'acyclovir, les considérations monétaires limitent l'utilité de ce médicament à un groupe restreint de patients. La névralgie postzostérienne nécessite une approche holistique associée à une pharmacothérapie comportant plusieurs classes de médicaments.

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HERPES ZOSTER (HZ), OR "shingles," produces an acute segmental neuralgia, which – although painful – is fortunately transient in most patients. Morbidity associated with this infection is more prevalent among the elderly and immunocompromised, particularly those who develop postherpetic neuralgia (PHN), a complication that could become a clinician's nightmare. This review discusses the clinical features and pharmacologic management of both these entities.

Epidemiology of HZ

Herpes zoster is a viral disease that occurs infrequently in young, healthy patients. However, its incidence rises sharply with age from an estimated 0.5 cases/1000 in children to five to 10 cases/1000 in individuals older than 80 years[1,2]; this phenomenon has been attributed to an age-related decline in cellular immunity.[3] Association with race, sex, ethnic background, or seasonal variations has not been reported for this disease.[2]

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In addition to the elderly, immunocompromised patients, particularly those suffering from hematologic or reticuloendothelial malignancies, have a greater risk of developing HZ.[4-6] Furthermore, HZ might be the first clinical manifestation of HIV infection. In a study among 48 HZ patients, 35 (73%) were seropositive for HIV on the initial day of diagnosis of HZ. Of these, 34 (97%) were known to be at high risk for AIDS.[7]

Therefore, among patients at risk for AIDS, the occurrence of HZ might precede the marked depression of cellular immunity associated with AIDS or AIDS-related complex. Similarly, a greater incidence of HZ has been reported in patients with rheumatoid arthritis receiving weekly, low-dose methotrexate therapy compared with the general population.[8] These observations show that HZ outbreaks are clearly dependent on the breakdown of normal immune surveillance.

Pathology of HZ

Acute varicella infection, usually a childhood disease (chicken pox) begins with viral entry through the oral or respiratory passages. Viremia and seeding of the skin then follows, and as the primary infection resolves, retrograde axonal transport of

the virus to the dorsal root ganglion cells gives rise to the latent (dormant) phase. When the host immune system is impaired, the latent virus might become reactivated, spreading within the ganglion to the skin and manifesting itself as HZ.[9]

Table 1. **Anatomic distribution**

REGION	CASES %
Thoracic	55
Cranial (trigeminal)	15
Lumbar	14
Cervical	12
Sacral	3
Disseminated	1

Adapted from Loeser.[10]

Acute HZ is characterized by inflammation, necrosis, and often hemorrhage in the involved dorsal root ganglion.

Clinical features

The dermatomal distribution of HZ can vary; the thoracic area is involved in more than half of all cases (*Table 1*[10]). The next most commonly affected dermatome is that supplied by the trigeminal nerve, and with advancing age the proportion of patients with consequent ophthalmic involvement increases. Disseminated zoster is a severe, generalized form of HZ resembling chicken pox. Only 1% to 8% of patients develop recurrences, and of these, half will occur at the site of the previous eruption.[9-11]

Before visible skin lesions develop, a prodromal phase typically occurs in which patients might describe sensations of tingling, burning, or itching. These symptoms appear to result from viral degeneration of cutaneous nerve fibrils. Pain or itch usually precedes the rash by several days or up to 2 weeks, although less commonly, pain might *follow* the eruption, or both occur simultaneously.[11,12] Similarly, pain without rash, or "zoster sine herpete," has been reported.[13]

The rash of acute zoster is typically erythematous and maculopapular and evolves to grouped vesicles within 24 to 36 hours. Constitutional symptoms of fatigue, malaise, headache, and low-grade fever might accompany the rash. The vesicles become pustular or hemorrhagic by the third or fourth day followed by drying and crusting in 7 to 10 days. Spontaneous resolution of the acute phase occurs in 2 to 3 weeks, with the crusts falling off, often leaving areas of residual scarring.[11,12]

Individuals who have never had chicken pox might develop the infection if exposed to a patient with acute HZ vesicles; however, it is extremely rare to acquire HZ solely from exposure to a patient with chicken pox.[14] Patients with disseminated zoster are a particularly contagious threat to an immunocompromised host. For this reason, HZ patients are well advised to observe isolation until their primary crusts have disappeared.[15]

Pain associated with HZ has been described as a continuous aching, itching, or burning, often with superimposed severe shooting sensations that might be precipitated by touching or moving the affected area. The region often becomes hyperesthetic, and the patient might complain of exquisite tenderness around vesicles that can worsen if ulceration and secondary infection ensue. Untreated pain can result in mood and behavioural changes, including disruption of sleep, diminished appetite, and social withdrawal. These symptoms can evolve into a pattern of abnormal illness behaviour and depression that is very common in patients with other forms of chronic nonmalignant pain.[11]

In younger patients, pain of acute HZ is not usually very debilitating and normally subsides as the rash resolves. Elderly patients, however, suffer more pain in the vesicular stage and are more likely to develop the most common and perhaps the most feared of complications, PHN. Possible complications of HZ are listed in *Table 2*.[2,12]

Pharmacologic treatment of HZ

Treatment of HZ in the acute stage should be directed toward minimizing patient discomfort; shortening the duration of symptoms; and preventing complications, such as PHN.

Topical agents. Local care is necessary for relieving itching and reducing bacterial colonization of damaged skin. This can be accomplished by using wet dressings or compresses soaked in tap water or 5% aluminum acetate (Burow's solution) and applied four to six times daily. Calamine lotion could then be applied lightly after removal of compresses.[10] Antibiotic creams or ointments are useful only for ulcerated lesions that have become infected secondarily. In one report, 42 patients treated with 1% silver sulfadiazine cream showed a definite clinical response against such types of infected lesions.[16]

Analgesics. Mild to moderately strong systemic analgesics, such as acetaminophen, codeine, and nonsteroidal anti-inflammatory drugs (NSAIDs) are generally effective in treating acute pain of HZ. No well-designed studies evaluate the efficacy of these agents for HZ, but clinical experience suggests that analgesics might lessen acute pain and encourage mobilization.[11,12,14]

Antivirals. Both intravenous and high-dose oral acyclovir have demonstrated activity against acute HZ.[17,18] In a multicentre, randomized, double-blind trial, 800 mg of oral acyclovir given five times daily for 7 days was compared with placebo in 205 immunocompetent patients with HZ older than 60 years of age.[18] Acyclovir accelerated the healing of lesions significantly and shortened the duration of viral shedding if treatment was initiated within 48 hours: ie, the time to loss of vesicles and full crusting was hastened by about 3 days as compared with patients on placebo. However, this perceived difference in healing time due to acyclovir was diminished in patients who did not receive treatment until 48 to 72 hours after onset of the rash.

In addition, acyclovir caused a significant reduction in pain scores during the acute stage (particularly among patients with severe pain), although a 6-month follow up failed to show a sustained decrease in incidence and severity of PHN.[19] In contrast, an earlier study employing a 10-day course of oral acyclovir at the same dose reported a significant reduction in the incidence of PHN but only if defined as pain occurring 1 to 3 months following acute HZ.[20]

While the effects of acyclovir in acute HZ are well documented, its role in PHN is less clear. Further research is required, perhaps to evaluate whether longer treatment courses of acyclovir will ultimately affect the development of PHN. Current guidelines for treating acute HZ suggest acyclovir therapy be initiated within 48 to 72 hours of onset, at an oral dose of 800 mg five times daily (every 4 hours while awake) for a total of 7 to 10 days. Dosage reduction is recommended for patients with acute or chronic renal impairment.[21]

Injectable acyclovir should be reserved for patients unable to tolerate the oral forms or for patients in whom aggressive therapy is indicated. At least 5 mg/kg intravenously every 8 hours has been used to treat uncomplicated HZ, while immunocompromised patients or patients with disseminated zoster, encephalitis, acute retinal necrosis, or other serious forms of HZ generally receive 10 mg/kg intravenously every 8 hours for 10 days.[18,22]

A recent study found oral acyclovir to be equally efficacious as intravenous acyclovir for treating localized HZ after bone marrow transplantation[23]; however, more studies are probably needed before oral therapy is universally accepted for treating this unique patient population. Although using acyclovir during acute uncomplicated HZ does not rule out the possibility of developing a more serious form of the disease (*Table 2*), once the diagnosis of disseminated zoster, zoster-associated encephalitis, or HZ ophthalmicus is apparent, acyclovir therapy is clearly indicated.[22] In the latter case, initiating oral acyclovir in nonimmuno-suppressed patients with acute HZ ophthalmicus prevents the ocular complications otherwise affecting up to 50% of untreated individuals.[24]

An important consideration related to systemic acyclovir therapy is cost. Ten days of oral therapy for HZ costs patients approximately $250. The economic impact of this drug must be weighed against the morbidity of zoster in a particular patient population; hence, routine use of acyclovir in young and immunocompetent individuals is unjustified. Conversely,

Table 2. **Complications of herpes zoster**

- Postherpetic neuralgia
- Meningoencephalitis
- Cerebrovasculopathy
- Cranial nerve syndromes
  - Trigeminal (ophthalmic) branch (HZ ophthalmicus)
  - Facial and auditory nerves (Ramsay Hunt's syndrome)
- Peripheral motor weakness
- Transverse myelitis
- Visceral involvement
  - Pneumonitis
  - Hepatitis
  - Pericarditis or myocarditis
  - Pancreatitis
  - Esophagitis
  - Enterocolitis
  - Cystitis
  - Synovitis
- Cutaneous dissemination
- Superinfection of skin lesions

Adapted from Ragozzino et al[2] and Carmichael.[12]

Table 3. **Pharmacologic management of postherpetic neuralgia**

CLASS/AGENT	DOSAGE	NOTES
TRICYCLIC ANTIDEPRESSANTS (ORAL)		
Amitriptyline	10 mg at bedtime (initial) 50-150 mg at bedtime (usual range)	Considered drug of choice
Doxepin	10 mg at bedtime (initial) 50-150 mg at bedtime (usual range)	Might be better tolerated in elderly due to reduced anticholinergic effects
ANTICONVULSANTS (ORAL)		
Carbamazepine	100 mg bid (initial) 200-1200 mg/d (usual range)	Useful for lancinating pain. Titrate dose until effect or side effect occurs. Serum level monitoring important for carbamazepine, phenytoin, and valproic acid
Phenytoin	15 mg/kg loading dose 200-400 mg at bedtime (maintenance)	
Valproic acid	250 mg daily (initial)	
Clonazepam	0.5 mg bid (initial)	
NEUROLEPTICS (ORAL)		
Fluphenazine	1-2 mg tid	Second-line agents because of risk of adverse effects and lack of controlled studies
Haloperidol	2-5 mg tid	
Pimozide	2 mg bid or tid	
TOPICAL		
Capsaicin 0.025% cream	Apply 3 or 4 times daily	Initial redness, burning, and stinging (transient)
EMLA® cream (lidocaine 2.5% and prilocaine 2.5%)	Apply every 12 h	
OTHER		
Baclofen	5 mg tid (initial)	Increase dose until effect or side effect occurs
Mexiletin	200-900 mg/d	Increase dose gradually. Gastrointestinal side effects very common

Adapted from Portenoy,[47] Duke,[49] Tanelian and Brose,[52] and Stow et al.[57]

immunocompromised patients with HZ, including the elderly and those on immunosuppressant drugs, as well as nonimmunocompromised patients exhibiting a serious manifestation of zoster are prime candidates for acyclovir therapy.

Acyclovir ointment has largely been abandoned in favour of the systemic forms of the drug. While it might accelerate cutaneous healing of HZ lesions, it is by no means a substitute for the oral or intravenous routes.[25] Topical acyclovir has also been investigated for use in HZ ophthalmicus; however, because it lacks appreciable ocular penetration, it is mainly prescribed for some patients as an adjunct to systemic therapy.[26]

Incidentally, Zovirax® (acyclovir) 5% ointment is not recommended for direct application to the eye or other mucous membranes.[27]

Other antiviral drugs have also been investigated in treating HZ, including amantadine[28] and vidarabine,[29] but the literature suggests that these have largely been replaced by acyclovir due to its greater activity, ease of administration, and relatively low toxicity.

Corticosteroids. Systemic corticosteroids are frequently advocated for use in HZ and PHN, but their precise role has not yet been fully elucidated. Two recent papers have reviewed the evidence for and against corticosteroid therapy by evaluating all well-designed studies reported in the English literature comparing systemic steroids with placebo in preventing PHN.[30,31] It appears that, while steroids might reduce early pain associated with HZ, and quite possibly decrease the proportion of patients affected by PHN (if defined as pain persisting 6 to 12 weeks after acute HZ), this benefit is not sustained when patients are followed beyond 3 months.

Intralesional and epidural steroids have also been purported to reduce the incidence of PHN, but no evidence from controlled studies is available to justify their routine use. Concern has been expressed regarding the use of steroids and the risk of disseminated HZ,[32] primarily in the context of patients with serious underlying disease or malignancy. Dissemination occurs in approximately 1% of otherwise normal patients, and thus in the young, nonimmunosuppressed population, a short course of high-dose steroid therapy might be warranted to reduce the duration of acute neuralgia; however, more studies employing sound methodology are needed to evaluate long-term effects on PHN.

In most clinical trials, 40 to 60 mg of oral prednisone daily has been administered for 7 to 10 days, followed by a gradual tapering over 2 weeks.[33-35] Despite the relative safety of short courses of corticosteroids, their indiscriminate use is not recommended. Only patients younger than 60 years of age with severe pain who do not have pre-existing conditions precluding the use of steroids should be considered for this treatment.

Cimetidine. Herpes zoster infection is known to be associated with a decline in cellular immunity.[3-8] Furthermore, it has been postulated that suppressor T cells carrying histamine H_2-receptors might play an important role in inducing immunosuppression as it relates to cancer and other disorders, including HZ. Cimetidine, a histamine antagonist, has been shown to reverse this immunosuppression and thereby favourably alter the clinical course of HZ.[36]

One study compared HZ patients receiving 400 mg of cimetidine taken orally three times daily with a control group receiving analgesics. Cimetidine was found to accelerate complete healing of cutaneous lesions significantly compared with the control group (12 versus 21 days, respectively), and to shorten the time to achieve onset of pain relief (3 versus 6 days), as well as complete pain resolution (14 versus 26 days).[37]

However, as only 16 patients were evaluated, it is difficult to predict the validity of these findings in the general population. While anecdotal reports show some intriguing results with cimetidine in HZ, well-designed, controlled studies to define its exact role are lacking.

Anesthetic approaches. Many uncontrolled studies have reported relief of acute pain following regional anesthesia. Local anesthetics have been administered into subcutaneous tissue, peripheral nerves, the

epidural space, the pleural space, and the paravertebral area.[38-42] A mixture of an anesthetic and a corticosteroid has also been used with favourable results.[43] Unfortunately, these reports are anecdotal, and although excellent results were claimed in some cases, the patient numbers are often too small and the period of follow up too brief to make valid conclusions.

Clinical experience using sympathetic blockade in acute HZ is fairly extensive, albeit uncontrolled, and might benefit immunocompromised patients who fail on acyclovir therapy or immunocompetent patients who fail on steroid therapy, particularly if performed within 2 weeks of the acute eruption.[9]

Epidemiology of PHN

The syndrome of PHN is characterized solely by the persistence of pain after HZ. Despite the need for accurate diagnosis, the point at which one becomes the other remains arbitrary. Postherpetic neuralgia has been variably defined as pain persisting at any point between the time of lesion healing (crusting) and up to 6 months later. This definition has important implications because it determines the point at which therapies for HZ should be abandoned for those appropriate for PHN.

Because PHN can spontaneously resolve with time, the choice of an interval to define the pain can influence the results of studies designed to evaluate its treatment. This must be kept in mind when assessing the results of the various treatments used for this disorder. A workable definition of PHN is usually pain persisting beyond 1 or 2 months after the acute stage of HZ.[1,2,11]

Overall, PHN occurs in about 9% to 14% of patients with HZ,[1,2] but the incidence increases to 50% in the elderly who also suffer more intense, longer lasting pain.[44] The pain of PHN is often qualitatively similar to that of HZ with some combination of burning, itching, or aching, accompanied sometimes by paroxysms of severe lancinating pain. Allodynia (pain from a nonnoxious stimulus) and hyperpathia (very unpleasant, exaggerated pain following a cutaneous stimulus) might be superimposed on the continuous component of the pain.[11]

Pathology of PHN

Both peripheral and central mechanisms seem to be involved in the pathogenesis of PHN. The current hypothesis is that HZ infection causes a preferential destruction of large (inhibitory) myelinated fibres and a more rapid regeneration of small (nociceptive or pain-producing) fibres resulting in an imbalance of sensory input.[45]

Pharmacologic treatment of PHN

Management of established PHN requires a multimodal, multidisciplinary approach, including pharmacologic, neuroaugmentative (eg, transcutaneous electrical nerve stimulation, counterirritation), anesthetic, psychiatric, psychologic, and surgical (eg, dorsal root entry-zone lesion) techniques (*Table 3*[47,49,52,57] and *Figure 1*[9]). Postherpetic neuralgia that persists beyond several years is generally regarded as being refractory to all therapies.[11]

Tricyclic antidepressants. Amitriptyline is considered the drug of choice for patients with PHN largely because of the results of a double-blind, placebo-controlled crossover study in which good to excellent pain relief was achieved by 16 of 24 patients receiving a median dose of 75 mg daily.[46] The analgesic effect of amitriptyline was believed to be independent of its antidepressant action (serum levels in responders were below the antidepressant therapeutic range) and might have been due, in part, to its sedative effect.

Because of the potential for anticholinergic side effects, most authorities recommend a starting daily dose of 10 mg for elderly patients with 10-mg increments every 5 to 7 days. Alternatively, doxepin[47] or desipramine[48] might be better tolerated by the elderly because of fewer anticholinergic effects.

Neuroleptics. The efficacy of neuroleptics in PHN remains unproven, yet drugs such as fluphenazine and haloperidol have been used in low doses in combination with antidepressants. Pimozide might benefit the PHN patient with neurotic tendencies, for example, a patient who presents with self-inflicted excoriations of painful skin.[49] It must be stressed, however, that the elderly, who constitute most

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patients with PHN, are at greater risk for developing adverse effects from this class of drugs. Therefore, neuroleptics should not be considered first-line agents for the elderly.

Anticonvulsants. Anticonvulsants, in particular carbamazepine, are effective in conditions, such as trigeminal neuralgia, that are characterized by lancinating pain.[50,51] For this reason, carbamazepine, phenytoin, valproic acid, and clonazepam might be useful for ameliorating the shooting component of the pain, while not necessarily affecting the continuous component. Side effects of these agents are often severe and dose-limiting; hence, serum level monitoring becomes necessary to ensure therapeutic, non-toxic concentrations of carbamazepine, phenytoin, and valproic acid.

Because carbamazepine stimulates its own metabolism, careful monitoring of levels with frequent increases in dose might be required. The combination of a tricyclic antidepressant and an anticonvulsant might be useful for patients with PHN who have both dysesthesia and lancinating pain.[11]

Baclofen. Baclofen, a muscle relaxant effective in trigeminal neuralgia, might also reduce lancinating pains associated with PHN.[47]

Mexiletin. Mexiletin is an antiarrhythmic that, by virtue of its ability to block sodium channels, has recently been found to be efficacious for treating neuropathic pain. Lidocaine shares the same electrophysiologic effect, which suppresses nerve conduction in pain-causing fibres. For this reason, lidocaine infusions have been used initially to predict response to oral mexiletin therapy.[52]

Topical agents. Capsaicin is a naturally occurring irritant compound found in the fruit of several members of the nightshade plant family and is commercially available as a 0.025% cream.[53,54] A double-blind, placebo-controlled study with 32 patients showed that almost 80% of individuals treated with capsaicin experienced reduction in pain after 4 to 6 weeks of therapy for PHN.[53]

Capsaicin is thought to act by depleting substance P (the primary chemomediator of painful impulses from the periphery to the central nervous system) from cell bodies and nerve terminals.[55] Because this agent has a very short duration of action, it is necessary to apply it at least three to four times daily to produce and maintain pain relief. Early in therapy, local burning, stinging, and redness are common but usually disappear with repeated applications. Results are generally noted within 14 days; however, the optimum length of capsaicin treatment is unknown.[53]

Local anesthetics applied topically have been reported to decrease PHN. Lidocaine 5% ointment and EMLA® cream (a eutectic mixture of lidocaine and prilocaine) under an occlusive dressing have both been shown to reduce pain in patients with PHN refractory to other therapies and might also require less frequent application than capsaicin.[56,57] Interestingly, pain relief outlasted the duration of local anesthesia in most patients.[56]

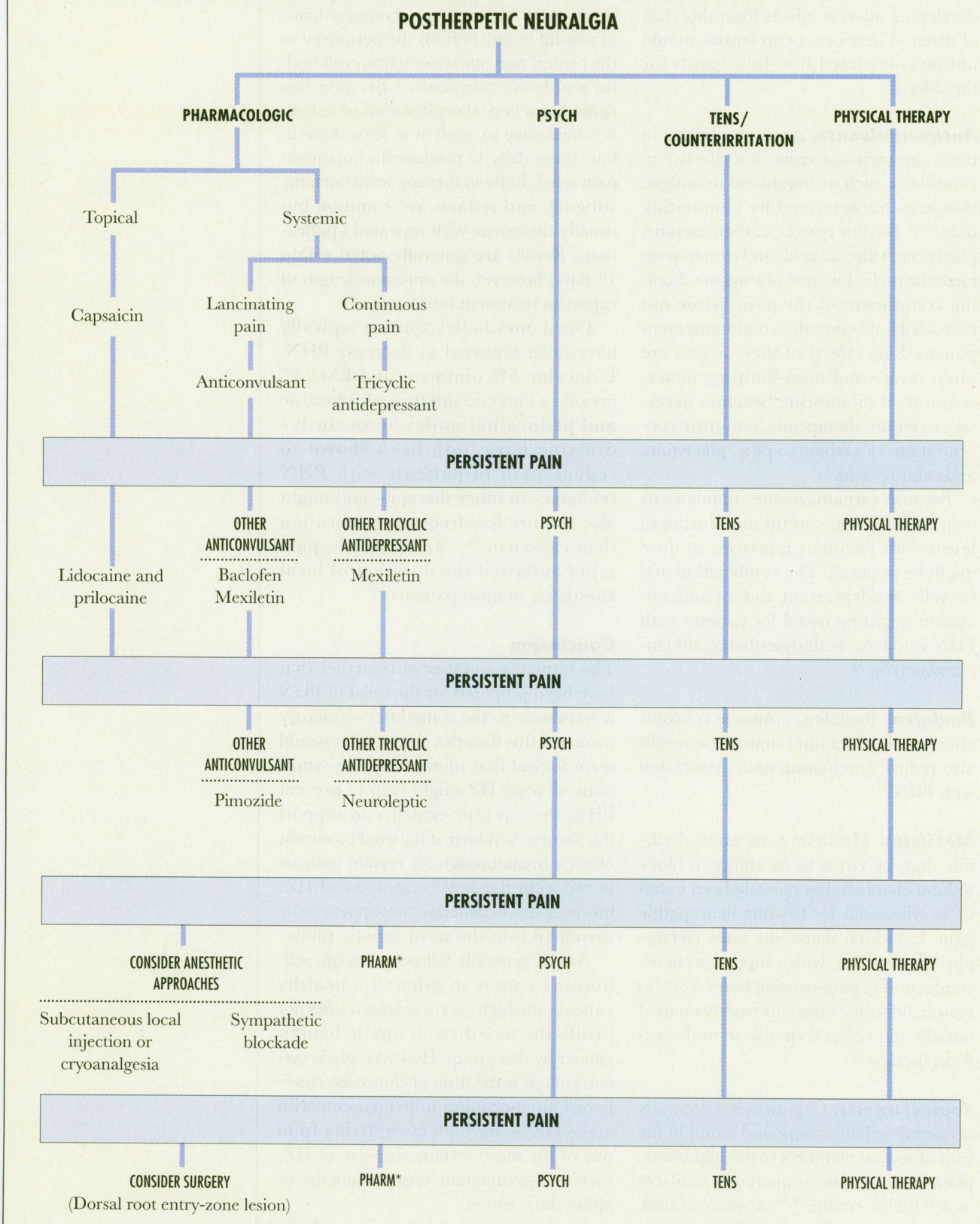
Conclusion

The immense number of remedies that have been proposed for the relief of PHN is testimony to the sometimes refractory nature of this disorder. Although it would seem logical that minimizing the symptoms of acute HZ might help to prevent PHN, there is little evidence to support this theory. Acyclovir, if initiated promptly, offers a breakthrough for certain patients in reducing the acute symptoms of HZ; however, this benefit does not appear to be sustained into the postherpetic phase.

As HZ generally follows a benign, self-limiting course in otherwise healthy patients, the high cost of acyclovir does not justify the less-than-dramatic benefit gained by this group. However, given systemically, it is the drug of choice for elderly or immunocompromised patients with acute HZ or for patients suffering from one of the more serious sequelae of HZ, such as dissemination, encephalopathy, or ophthalmic zoster.

Oral corticosteroid therapy might be considered where severe neuralgia is present during HZ; however, it, too, might not affect the course of PHN, particularly if the period of patient follow up is long.

Figure 1. **Algorithm for managing established postherpetic neuralgia (multimodal approach)**



PSYCH – *psychologic or psychiatric support,* **TENS** – *transcutaneous electrical nerve stimulation,* **COUNTERIRRITATION** – *brisk rubbing of painful area often preceded by applying a cooling spray,* **PHARM** – *pharmacologic therapy.*

**any pharmacologic agent that has proven even minimally efficacious should be continued.*

Adapted with permission from Galer and Portenoy.[9]

Conservative management of patients using good local skin care and over-the-counter analgesics might be the best strategy in most HZ cases.

Once PHN is established, a multimodal, multidisciplinary approach is indicated as with many other chronic pain syndromes. Amitriptyline, capsaicin, and possibly carbamazepine (if pain has a shooting quality) are wise pharmacologic choices, at least in the preliminary phase of treatment. ■

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